REMARKS

Claims 1-5 remain pending in the instant application. Claim 1 is amended to indicate that the recited antibody is an isolated antibody. Support for the amendment can be found, for example, at paragraphs [0246] and [0402] of the specification and in the claims as originally filed. Applicants respond below to the specific rejections set forth in the Office Action mailed December 23, 2004, and the Advisory Action mailed June 21, 2005.

Priority

The PTO asserts that the earliest priority date for the present application is its filing date, May 3, 2002.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. Applicants submit that for the reasons stated herein, the claimed antibodies are enabled by the disclosure of PCT/US00/23328 and have a credible, substantial, and specific utility. In view of that, Applicants maintain that the present application is entitled to at least the priority date of August 24, 2000, the filing date of PCT/US00/23328.

Rejection under 35 U.S.C. §101 – Utility

The PTO has maintained the rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking patentable utility. The PTO argues that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons of record on pages 3-8 of the first Office Action.

The PTO argues that "the Specification provides data showing a very small increase in DNA copy number – about 2 fold – in one cancer tissue and one normal tissue." The PTO further states that "there is no evidence regarding whether or not PRO1328 mRNA or polypeptide levels are also increased in these tissues." The PTO relies upon Pennica et al. (PNAS 95:14717-14722 (1998)) as support for the proposition that "what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels." The PTO also argues that Haynes et al. (Electrophoresis 19:1862-1871 (1998)) teaches that polypeptide levels cannot be accurately predicted from mRNA levels. Furthermore, the PTO asserts that there is no correlation between gene expression levels and the role of the molecule in disease relying upon Hu et al. (Journal of Proteome Research 2:405-412 (2003)). The PTO concludes that given "the

small increase in DNA copy number" and the above-mentioned literature references, "it is clear that one of skill in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels."

Furthermore, the PTO discounts the previously-submitted Declarations by Ashkenazi, Grimaldi, and Polakis. The PTO argues that there is no evidence whether the gene products are over-expressed or not. The PTO argues that the specification "provides no information regarding increased protein, DNA or mRNA levels of PRO1328 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented and then only in one normal tissue and one unrelated tumor tissue." The PTO makes other arguments based upon the mistaken assertion that only gene amplification data are provided.

Applicants respectfully disagree and submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to an Absolute Certainty – a Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ

885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty,

rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. IIzuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. IIzuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween".

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

*The Data in Example 18 are Data Regarding Differential mRNA Levels, **not** Gene Amplification*

In the Final Office Action the PTO incorrectly argues that there is no utility based upon the incorrect assertion that the specification only provides data showing an increase in DNA copy number, and that the specification provides no information regarding mRNA levels of PRO1328 in tumor samples compared to normal tissue samples. Respectfully, the PTO's arguments are incorrect.

Applicants clarify that the data concerning the differential expression of the PRO1328 gene presented in Example 18 relate to gene expression, **not** gene amplification. The description of Example 18 makes clear that the results were obtained by quantitative PCR amplification of cDNA libraries. It is well known in the art that cDNA libraries are made from mRNA, and reflect the level of mRNA for a particular gene in the source tissue. Thus, Example 18 reports a measure of the *expression* of the PRO1328 gene, i.e. mRNA levels, not its *amplification*, i.e. the number of copies of PRO1328 in the genome. The data in Example 18 show differential mRNA expression between cancerous and non-cancerous tissue. Specifically, the data in Example 18 show increased mRNA levels of the gene for PRO1328 in normal lung tissue compared to lung tumor tissue, and increased mRNA levels in melanoma tissue compared to normal skin tissue. Furthermore, as set forth more fully below, the differential mRNA expression would be understood by the skilled artisan to also correlate with differential expression of the PRO1328 polypeptide.

The PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Also, Applicants submit that any lack of correlation between gene amplification and gene expression is not at issue in this application and therefore the Pennica et al. reference is not relevant.

Applicants have established that the Gene Encoding the PRO1328 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1328 gene is differentially expressed in lung tumors and melanoma tissue. The gene expression data in Example 18 show that the mRNA associated with protein PRO1328 was more highly expressed in normal lung tissue and melanoma tissue versus lung tumor and normal skin tissue. Gene expression was analyzed using standard semi-quantitative PCR amplification reactions of cDNA libraries isolated from different human tumor and normal human tissue samples. Identification of the differential expression of the PRO1328 polypeptide-encoding gene in tumor tissue compared to the corresponding normal tissue renders the molecule useful as a diagnostic tool for the determination of the presence or absence of tumor. Applicants previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual. That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue

and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

The PTO has stated that the Grimaldi Declaration is insufficient to overcome the rejection of Claims 1-5. First, the PTO states that "it is important to note that the instant specification provides no information regarding increased protein, DNA or mRNA levels of PRO1328 in tumor samples ... [o]nly gene amplification data were presented and then in only one normal tissue and one unrelated tumor tissue." The PTO also makes various arguments in support of the Grimaldi Declaration being insufficient based upon an alleged lack of association between the PRO1328 gene and cancer, particularly lung and skin cancers. The PTO also argues that it is not known whether PRO1328 is expressed in cancerous lung or normal melanocytes or skin tissue, and what the relative levels of expression are. Further, the PTO states that "one cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in copy number, or alternatively due to increase in transcription rates."

As discussed above, the specification and the first Grimaldi Declaration make clear that Example 18 used quantitative PCR of cDNA libraries. Therefore, one of skill in the art would know that Example 18 is a measure of mRNA levels, and reflects differential PRO1328 gene expression, not gene amplification. It is irrelevant whether this is due to an increase in copy number or an increase in transcription rates. Pennica et al. is irrelevant to the instant application that reports differential gene expression, not gene amplification, and therefore, does not support the PTO's challenge of the sufficiency of the Example 18 data, or the first Grimaldi Declaration.

Also, a gene or a polypeptide that is differentially expressed in cancerous compared to non-cancerous tissue has utility as a cancer marker regardless of whether the molecule is associated with tumor formation or the development of cancer. Here, all that is necessary to show for purposes of utility is that there is different expression of the molecule in cancerous tissue versus non-cancerous tissue of the same type.

Furthermore, contrary to the PTO's assertions, relative levels of expression are shown. In fact, the data in Example 18 relate to relative levels in cancerous versus non-cancerous tissue. This is supported by the first Grimaldi Declaration in which Mr. Grimaldi explained that "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, the specification provides relative levels of expression. The precise levels of expression in normal tissue are irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As stated by Mr. Grimaldi, "any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue" and that the genes of interest "can be used to differentiate tumor from normal." The arguments raised by the PTO do not contradict the utility of the instant claims.

Applicants have established that the Accepted Understanding in the Art is that there is a Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1328 polypeptide in lung and melanoma tumor, it is more likely than not that the PRO1328 polypeptide is differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and

treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the previously submitted teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994), and Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002). Figure 9-2 of Alberts 3rd ed. shows the steps at which eucarotic gene expression can be controlled. The first step depicted is transcriptional control. Page 403 of Alberts 3rd ed. provides that "For **most genes** transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Page 453 of Alberts 3rd ed. provides that "Although **controls on the initiation of gene transcription are the predominant form of regulation for most genes**, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Thus, as established in Alberts 3rd ed., the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Alberts 4th ed., Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes

according to the needs of the moment – *most obviously by controlling the production of its mRNA*." *Id.* at 302, emphasis added. Similarly, figure 6-90 on page 364 of Alberts 4th ed. illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "**the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes**." *Id.* at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "**[f]or most genes transcriptional controls are paramount**." *Id.* at 379.

Further support for Applicants' position can be found in previously submitted Lewin textbook, Genes VI, which states that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription."

Additional support is found in the previously submitted publication by Zhigang et al., World Journal of Surgical Oncology 2:13, 2004. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" (see Zhigang, page 4). Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Zhigang at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Zhigang at 7.

Further, the previously submitted publication by Meric et al., Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric et al. at 971 (emphasis added).

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicants submit that a lack of known role for PRO1328 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known physiological role of PRO1328, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1328 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer and antibodies that bind the proteins have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See, e.g.,* U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 attached hereto as Exhibits 1-4.)

In response to the second Grimaldi Declaration and the Polakis Declaration, the PTO states that "it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1328.... Only gene amplification data were presented." The PTO concludes that the declaration is insufficient to overcome the rejection of claims 1-5 ... "since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels." Office Action at 9.

Applicants again reiterate that Example 18 is information regarding differential mRNA levels of PRO1328. Thus, the PTO's rejection of the Polakis Declaration because it discusses the correlation of mRNA levels and polypeptide levels is misplaced.

Accordingly, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1328 mRNA is more highly expressed in normal lung tissue and melanoma tissue compared to lung

tumor tissue and normal skin tissue, respectively, the PRO1328 polypeptide will also be more highly expressed in normal lung tissue and melanoma tissue compared to lung tumor tissue and normal skin tissue, respectively. This differential expression makes the PRO1328 polypeptides and antibodies to them useful as diagnostic tools for cancer.

The References cited by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

The PTO relies on two references, Haynes et al. and Hu et al., for support of the proposition that polypeptide levels cannot be accurately predicted from mRNA levels, and that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

The PTO cites Haynes et al. (Electrophoresis, 19(11):1862-71 (1998)) as support for the assertion that "polypeptide levels cannot be accurately predicted from mRNA levels, and that according to their results, the ratio varies from zero to 50-fold." Office Action at 4.

Haynes is a review article dealing with the art of proteome analysis. The assertions in Haynes cited by the Examiner were made in an effort to identify shortcomings in the art of mRNA quantification to argue for "proteome analysis to become an essential component in the comprehensive analysis of biological systems." Haynes, p. 1863. Haynes studied 80 selected samples from *Saccharomyces cerevisiae*, and reported "a general trend but no strong correlation between protein and transcript levels (Fig. 1)." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, previously submitted publication by Gygi et al., Molecular and Cellular Biology, Mar. 1999, 1720-1730. Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi, p. 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *See id.* Considering that Example 18 of the specification shows higher expression of PRO1328 mRNA in normal lung and melanoma tissue as compared to lung tumor and normal skin tissue, Haynes and Gygi actually provide strong evidence in

support of a general correlation between mRNA and protein levels, and thus further support the utility of the PRO1328 polypeptides and the claimed antibodies to the same.

The 50-fold variation referred to by Haynes and cited by the Examiner, does not in any way show the absence of a correlation between mRNA and protein levels, but rather identifies the outer limits of variability in the authors' experiments. This variability may support the authors' assertion that the amount of a particular protein cannot accurately predict the particular level of the corresponding mRNA transcript, but it does not suggest an absence of a general correlation between mRNA and protein levels. Again, Applicants' utility is based on the differential expression of mRNA in normal skin and normal lung versus melanoma and lung tumor. Exact levels of expression are irrelevant. Moreover, Gygi states that the high degree of variability seen at low levels of mRNA (shown in inset of Fig. 1, Haynes p. 1863) is due to the fact that "the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA levels." Gygi, p. 1727. Considering that PRO1328 mRNA has been shown in Example 18 of the specification to be more highly expressed in melanoma tissue than normal skin tissue, and in normal lung tissue than in lung tumor, the variability identified by Haynes is even less applicable to establishing the absence of a correlation between mRNA and protein levels in the instant case.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Here, the utility requirement does not require Applicants to show that mRNA levels correlate to protein levels in every case, but rather only that the correlation exists more often than not. The data presented in Haynes is not inconsistent with or contradictory to the utility or enablement of the instant claims. To the contrary, the data clearly show a general correlation between protein levels and mRNA levels, and thus support Applicants' assertion that such a general correlation exists.

Even if Haynes supported the Examiner's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented above by Applicants, is that there is a direct correlation between mRNA levels and protein levels. This is further supported by the statement in Haynes that "interpretations of quantitative mRNA expression profiles frequently implicitly or explicitly assume that for specific genes the transcript levels are

indicative of the levels of protein expression." See, Haynes, p. 1863, first full paragraph. Haynes does not suggest there is no correlation between mRNA and protein levels, but rather points to what the authors believe are shortcomings of using mRNA quantification to predict protein levels; specifically, that mRNA levels may not accurately predict protein levels *in each particular instance.* Considering the more likely than not standard for utility, Haynes' identification of reasons why proteomic analysis may be preferable in some cases does not contradict Applicants' evidence that there is a general correlation between mRNA and protein levels.

The PTO cites Hu et al. (J. Proteome Res., 2(4):405-12 (2003)) for support for the conclusion that not all genes with increased expression in cancer have a known or published role in cancer. Like Haynes, this reference is in no way contrary to or inconsistent with Applicants' asserted utility.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and

reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as molecular markers of cancer.

Applicants submit that a lack of known role for PRO1328 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1328 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

As stated above, the standard for establishing a use for a claimed invention is not absolute certainty, and thus a *necessary* correlation between mRNA levels and protein levels is not required.

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

There is nothing in the cited references that casts any doubt on the Applicants' assertion that in general, there is a positive correlation between changes in mRNA level and protein level. Haynes et al. and Hu et al. are not sufficient to satisfy the PTO's burden of offering evidence that a person of skill in the art would have a reasonable doubt that antibodies to a polypeptide differentially expressed in certain tumors can be used as a diagnostic tool since neither reference addresses this issue. Given the lack of support for the PTO's position, and the supporting evidence provided by the Applicants for their position, one of skill in the art would be more likely than not to believe that the claimed antibodies to the PRO1328 polypeptide can be used as diagnostic tools for cancer, particularly lung and skin cancer.

Conclusion

The PTO has asserted three arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that the increase in gene amplification of PRO1328 would correlate with increased mRNA or polypeptide levels: (1) the PTO has challenged the reliability of the evidence reported in Example 18; (2) the PTO cites Pennica et al. to support its position that gene amplification is not necessarily correlated to gene expression; and (3) the PTO cites Haynes et al. and Hu et al. to support its assertion that mRNA levels are not predictive of protein levels, and that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO states that further research needs to be done to determine if the increase or decrease in PRO1328 DNA supports a role for the peptide in cancerous tissue. Applicants have addressed each of these arguments in turn.

First, Applicants have pointed out that the data in Example 18 reflect gene expression levels, not gene amplification levels. Further, Applicants previously provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the relative difference in mRNA expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the previously submitted second Grimaldi Declaration and the previously submitted Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references.

Third, the Applicants have shown that the references cited by the PTO to support its conclusion that polypeptide levels cannot be accurately predicted from mRNA levels, and that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, are not contrary to Applicants' asserted utility. These references do not satisfy the PTO's burden of offering evidence to prove that one of skill in the art would reasonably doubt the asserted utility.

Applicants submit that one of skill in the art is more likely than not to believe that the PRO1328 polypeptide is differentially expressed in certain tumors given the mRNA expression patterns shown in Example 18. Applicants have therefore established the utility of the claimed antibodies since one of skill in the art will recognize that antibodies to a polypeptide differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as a diagnostic tool. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1328 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO has maintained the rejection of Claims 1-5 as lacking enablement under 35 U.S.C. § 112, first paragraph. According to the Examiner, because the claimed invention is not

supported by either a substantial asserted utility or a well established utility, one of skill in the art would not know how to use the invention.

Applicants believe that the evidence, declarations, references, and arguments discussed above make clear that Applicants have established that one of skill in the art would be convinced, to a reasonable probability, that PRO1328 polypeptides are overexpressed in normal lung tissue and melanoma tissue, and therefore, the claimed antibodies have utility as diagnostic tools for screening tissue to detect lung and melanoma tumors. The techniques for the creation of antibodies are well known and routine in the art. Thus, at least one use of PRO1328 nucleic acids, the polypeptides and the claimed antibodies is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. 2164.01(c). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 20, 2005

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